REMARKS

Claims 72-91 are pending in the present application. Claims 72-91 are rejected. Applicants respectfully disagree with the rejections and submit the following remarks in response thereto.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 72-91 were rejected under 35 U.S.C. § 112, first paragraph, the Office Action alleging that the specification does not enable a person skilled in the art to which it pertains, or to which it is most nearly connected, to make and use the invention commensurate in scope with the claims. The Office Action admits that the specification is enabling for (1) a method of obtaining a sustained CTL response in a mammal, which method comprises delivering tumor specific antigen such as the ones disclosed on page 21, virus specific antigen LCMV p33, directly to a lymph node or a lymph vessel of the mammal at a level sufficient to induce a CTL response in the mammal and maintaining the antigen in the mammal's lymphatic system over time to sustain the CTL response. However, the Office Action alleges that the specification, does not reasonably provide enablement for *any* method of obtaining a sustained CTL response as set forth in claims 72-91 for treating *any* disease such a cancer, chronic infectious disease such as hepatitis, and AIDS.

To be enabling, "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. M.P.E.P. § 2164.08 (citing *In re Buchner*, 929 F.2d 1557 (Fed. Cir. 1993)). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Regarding the Office Action's assertion that there is insufficient guidance as to the structure of the antigen used in the claimed method, Applicants respectfully submit that the

specification teaches one of skill in the art how to perform the full scope of the claimed methods. Applicants submit that the claimed methods of obtaining a sustained CTL response are not limited to any particular antigen, and thus, *any* antigen can be used in the claimed methods. Nevertheless, the specification provides numerous exemplary antigens that can be used with the claimed methods. *See, e.g.*, Specification at page 17, line 26 through page 22, line 6, and Tables I and II. Performance of the claimed methods does not require a particular antigen protein structure or protein function as suggested in the Office Action. Structure and function are largely irrelevant to the immunogenicity of an antigen, as exemplified by the fact that those of skill in the art often use denatured proteins as antigens. Because the claimed methods do not depend on protein structure or function, *any* antigen may be used. Accordingly, a person of skill in the art would be able to perform the claimed methods without undue experimentation.

Regarding the Office Action's assertion that the specification does not provide sufficient guidance for the terms "component" and "disease matched antigen," Applicants respectfully submit that a person of ordinary skill in the art, having read Applicants' disclosure, would be able to perform the claimed methods using such antigens. As discussed above, Applicants have fully enabled the claimed methods, and the methods are not limited to any particular antigen. The specification discloses that antigens useful in the claimed invention are those that stimulate the immune system of a mammal to destroy the pathogen causing the disease. Specification at page 17, lines 27-29. A person of ordinary skill in the art would understand the term "component of a microorganism cell" to refer to any constituent element of a microorganism cell capable of inducing an immune response, and the term "disease matched antigen" to refer to an antigen that is matched to the specific disease found in the animal being treated, as disclosed in the specification on page 17, lines 30-31. Such antigens are known in the art to stimulate the immune system of a mammal. Thus, a person of ordinary skill in the art, having read Applicants' disclosure, would be able to identify a component of a microorganism cell or a disease matched antigen that is able to stimulate the immune system of a mammal, and thus would be able to perform the claimed methods of obtaining a sustained CTL response using a component of a microorganism cell or a disease matched antigen without undue experimentation.

Regarding Claim 80, the Office Action asserts that there is insufficient guidance with respect to the assay used to detect the sustained CTL response in an animal. Specifically, the Office Action asserts that there is insufficient guidance as to which specific cytokine assay is

used, or as to how increasing life expectancy or observing the health of a mammal correlates with the sustained CTL response, or as to what is being detected using said immunofluorescence assay that is correlated with a sustained CTL response. Applicants respectfully submit that assays used to detect the presence of an immune response are known in the art. Thus, a person of ordinary skill in the art, having read Applicants' disclosure, would know how to use such assays to determine whether a sustained immune response has been obtained. For example, a person of ordinary skill in the art would recognize that obtaining a sustained CTL response would lead to increased life expectancy and/or improved health of the animal. Likewise, a lack of improved health of the animal would indicate that a sustained CTL response has not been obtained. Nevertheless, Applicants have provided examples of such assays throughout the specification, particularly at page 11, line 30 through page 13, line 16, and Examples 1-5. Thus, a person of ordinary skill in the art would be able to perform the claimed methods without undue experimentation.

With regard to Claim 85, the Office Action asserts that the specification does not define "patient-matched antigen" and that the specification discloses only HLA matched antigen. Applicants respectfully disagree and submit that one of skill in the art, having read Applicants' disclosure, would understand how to perform the claimed methods using a patient-matched antigen. As discussed above, Applicants have fully enabled the claimed methods of obtaining a sustained CTL response, and such methods are not dependent on any particular antigen. A person of ordinary skill in the art would understand the term "patient-matched antigen" to indicate that the antigen is matched to a particular patient, and would recognize that such an antigen would stimulate the immune system of the patient. Nevertheless, Applicants define and provide an example of how to obtain such an antigen in the specification at page 18, lines 1-26. Thus, a person of ordinary skill in the art would be able to identify a patient-matched antigen that is able to stimulate the immune response of the patient, and therefore would be able to perform the claimed methods using a patient-matched antigen without undue experimentation.

With regard to Claim 81, the Office Action asserts that use of an "adjuvant" in the claimed method contradicts the disclosure which provides that a fundamental improvement over the prior art is that it facilitates the use of inherently non-immunogenic peptide antigens for CTL stimulation without the combined use of conventional adjuvants. The Office Action correctly notes that the use of the claimed methods without the combined use of conventional adjuvants is

one of several improvements of the claimed invention. However, the Office Action incorrectly characterizes the use of adjuvants in Claim 81 as contradictory to the disclosure. While the claimed methods *can* advantageously be used in the absence of conventional adjuvants, the use of conventional adjuvants is not precluded by the claimed invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Finally, the Office Action asserts that there is insufficient *in vivo* data demonstrating that the claimed method can treat any disease such as AIDS, common cold, influenza, and cancer. Thus, in effect, the Examiner has required *in vivo* data for each embodiment of the invention in order to allow the claims, which is an improper standard given the data provided in the specification. The M.P.E.P. states that because only an enabling disclosure is required, the Applicant need not describe all actual embodiments. M.P.E.P. §2164.01(c). Applicants respectfully submit that the claimed methods of obtaining a sustained CTL response are disclosed in such a manner that one skilled in the art would be able to practice these methods without an undue amount of experimentation. Applicants disclose that the claimed methods are useful for treating any disease to which the animal's immune system mounts a cell-mediated response to a disease-related antigen in order to attack the disease. Specification at page 15, line 10-12. Applicants submit that a person of ordinary skill in the art would recognize diseases such as AIDS, common cold, influenza, and cancer as diseases to which an animal's immune system mounts a cell-mediated response to a disease-related antigen. Furthermore, Applicants submit that one of skill in the art would recognize that the *in vivo* results provided in the specification with regard to the LCMV antigen can be extrapolated across the entire scope of the claims. That is, the same methods used to obtain a sustained CTL response against the LCMV antigen can be used to obtain a sustained CTL response against any number of antigens. Furthermore, those of skill in the art would accept the successful use of the claimed methods in mice as establishing a significant probability that the claimed methods would be successful for use in humans. In view of the data showing the efficacy of the claimed methods in obtaining a sustained CTL response to LCMV in mice, and therefore, in view of the support in the specification for the invention as claimed, withdrawal of this rejection is respectfully requested.

In light of the foregoing remarks, Applicants submit that the specification reasonably provides enablement for a method of obtaining a sustained CTL response as set forth in Claims 72-91. Applicants respectfully request that all rejections under this section be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph -- Written Description

The Office Action has rejected Claims 72-91 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In particular, it is alleged that "the specification does not reasonably provide a written description of *any* method of obtaining a sustained CTL response as set forth in Claims 72-91 for treating *any* disease such as cancer, chronic infectious disease such as hepatitis, and AIDS."

To satisfy the written description requirement, a patent application must describe the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor was in possession of the claimed invention at the time the application was filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Possession may be shown in a variety of ways including description of an actual reduction to practice by describing testing of the claimed invention. M.P.E.P. § 2163 (citing *Enzo Biochem*, 296 F.3d 1316, 1326 (Fed. Cir. 2002)).

The Office Action alleges that there is insufficient written description about the structure associated with the function of any antigen, and that given the indefinite number of antigens, there is inadequate written description about the "antigen," including the "patient-matched antigen" and the "disease matched antigen." The Office Action asserts that a method of inducing a CTL response toward any undisclosed antigen is not adequately described, and that given the lack of any additional species of antigen encompassed by the claimed methods, one of skill in the art would conclude that the disclosure fails to provide a representative number of species to describe the genus.

Applicants respectfully disagree and submit that the claimed methods have been described in sufficient detail that one of skill in the art could conclude that the Applicants were in possession of the claimed invention at the time the application was filed. The claimed methods are directed to using an antigen to obtain a sustained CTL response in a mammal. Thus, the claimed invention is not limited to any particular antigen. Describing all antigens that could be used in this way is not the proper standard for written description of a method claim. Nevertheless, Applicants note that numerous exemplary antigens are disclosed throughout the specification, see for example, page 17, line 26 through page 22, line 6 and Tables I and II. Moreover, in addition to listing numerous antigens contemplated for use in the claimed methods, the specification discloses that an antigen useful in the invention is one "that stimulates the immune system of a mammal having a malignant tumor or infectious disease to attack the tumor and inhibit its growth or to destroy the pathogen causing the disease." Specification at page 17, lines 27-29. Therefore, the specification describes the full scope of the claimed methods, including numerous antigens that can be used with the claimed methods.

With regard to Claim 80, the Office Action alleges that there is inadequate written description for which cytokine is to be used in the "cytokine assay," and which molecule is to be detected using the "immunofluorescence assays" or "CTL assays" for a sustained CTL response in a mammal. Claim 79, from which Claim 80 depends, is directed to obtaining a sustained CTL response, wherein the sustained CTL response is detected in the mammal. The claim is not limited to any particular mode of detecting the sustained CTL response, thus, any means of detecting the CTL response may be used. Describing all means of detecting the CTL response is not the proper standard for written description of a method claim. Applicants respectfully submit that assays used to detect the presence of an immune response are known in the art. Nevertheless, Applicants have provided examples of such assays throughout the specification, particularly at page 11, line 30 through page 13, line 16, and Examples 1-5. Therefore, the specification describes the full scope of the claimed methods, including numerous assays that can be used with the methods.

With regard to Claim 85, the Office Action asserts that the specification does not define "patient-matched antigen." As discussed above, the claimed methods are not dependent on any particular antigen. A person of ordinary skill in the art would understand the term "patient-matched antigen" to indicate that the antigen is matched to a particular patient, and would

recognize that such an antigen would stimulate the immune system of the patient. Nevertheless, Applicants define and provide an example of how to obtain such an antigen in the specification at page 18, lines 1-26. Accordingly, Applicants respectfully submit that the specification describes the full scope of the claimed methods, including patient-matched antigens that can be used with the claimed methods.

With regard to Claim 81, the Office Action asserts that the "adjuvant" in the claimed method direction contradicts the disclosure. The Office Action correctly notes that the use of the claimed methods without the combined use of conventional adjuvants is one of several improvements of the claimed invention. However, the Office Action incorrectly characterizes Claim 81 as contradicting the disclosure. Applicants respectfully note that while the claimed methods may advantageously be used in the absence of conventional adjuvants, the use of conventional adjuvants is not precluded by the claimed invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

In light of the foregoing remarks, Applicants submit that Claims 72-91 meet the written description requirement of 35 U.S.C. § 112. Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 112, first paragraph -- New Matter

The Office Action has rejected Claims 80 and 84 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Specifically, the Office Action asserts that the "cytokine assay, an immunofluorescence assay, a tumor growth inhibition assay, tumor size reduction assay, a CTL assay, inhibition of tumor metastasis, increase in life expectancy, infectious disease recovery and observation of health of the mammal" in Claims 80 and 84 represents a departure from the specification and the claims as originally filed. Applicants respectfully submit that these terms are described in a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention. For example, Applicants describe numerous assays useful in detecting a sustained

CTL response, for example, in the specification at page 11, line 30 through page 13, line 16 and Examples 1-5. Thus, Applicants submit that Claims 80 and 84 are not a departure from the specification and claims as originally filed.

In addition, the Office Action asserts that the "acellular composition" in Claims 87-91 has no support in the specification and the claims as originally filed. Applicants respectfully disagree and submit that support for the term "acellular composition" can be found in the specification, for example, at page 13, line 17 through page 14, line 4. Thus, Applicants submit that the term has been described in a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention.

In light of the foregoing remarks, Applicants respectfully request that all rejections under this section be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph -- Indefiniteness

The Examiner has rejected Claims 74, 81-82, and 87-91 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action alleges that "component of a microorganism cell" in Claim 74 is indefinite and ambiguous because it is not clear if the "component" is referring to the DNA, the protein, or the cell wall of the microorganism or cell. In addition, the Office Action asserts that the "adjuvant" in Claim 81 is indefinite and ambiguous because the specification specifically discloses that the claimed method does not require adjuvant. Finally, the Office Action asserts that the "area of high lymphatic drainage" in Claims 82 and 87 is ambiguous and indefinite because the specification does not define said area.

Regarding the objection to the term "component" in Claim 74, Applicants respectfully disagree and submit that the term "component" clearly establishes the metes and bounds of the claim. The ordinary meaning of the term "component" is "a constituent element, as of a system." Accordingly, Applicants respectfully submit that one skilled in the art having read Applicants' disclosure could readily determine the metes and bounds of the claimed invention. Specifically, a person of skill in the art, reading the phrase "component of a microorganism cell" would

recognize that any constituent element of a microorganism cell capable of inducing an immune response would be encompassed by this phrase.

With regard to Claim 81, the Office Action objects to the term "adjuvant" because the specification discloses that the claimed method does not require adjuvant. The Office Action is correct that the combined use of conventional adjuvants is not required in practicing the claimed invention. However, Applicants note that while the claimed methods may advantageously be used in the absence of conventional adjuvants, the use of conventional adjuvants is not precluded by the claimed invention. Accordingly, Applicants respectfully request that this objection be withdrawn.

Regarding the objection to the term "area of high lymphatic drainage" in Claims 82 and 87, Applicants respectfully submit that it is clear from the specification, for example, at page 60, line 28 through page 61, line 1, that the term "area of high lymphatic drainage" is intended to refer to an area where relatively high lymphatic drainage occurs. In addition to defining what is meant by the term, Applicants provide guidance as to how to determine where this area would be for a particular patient. Accordingly, Applicants respectfully submit that one skilled in the art having read Applicants' disclosure could readily determine the metes and bounds of the claimed invention.

Rejection Under 35 U.S.C. § 102

The Office Action has rejected Claims 72, 74, 79-80, 82-84, 87, 89, 90 and 91 under 35 U.S.C. § 102(b), as being anticipated by Issekutz *et al.*, *Clin Exp Immunol* 56(3):515-23 (1984) (Issekutz).

The Office Action has also rejected Claims 79-80, 83, 86, 87, and 90 under 35 U.S.C. § 102(b), as being anticipated by Grohmann *et al.*, *J Immunol Methods* 137(1):9-15 (1991) (Grohmann).

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no

difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Independent Claims 72, 79, 82, 83, and 87 recite, in relevant part, "a method of obtaining a sustained CTL response in a mammal." Thus, obtaining a sustained CTL response is a meaningful feature of the claims, and therefore, must be considered in evaluating the patentability of the claims. Applicants respectfully submit that the cited references do not teach every element of the claims because none of the references teaches, *inter alia*, obtaining a sustained CTL response. Accordingly, Applicants submit that the cited references do not anticipate the claims.

Review of CTL Response Kinetics

As explained more fully below, the phrase "sustaining an immunologic CTL response" would be recognized by the skilled artisan to refer to a prolonged phase of effector CTL in the cytolytic immune response. CTL occur in several different states, each with different cytolytic potentials. In contrast to effector CTL, which possess cytolytic activity, naïve CTL and memory CTL only acquire cytolytic activity upon stimulation or restimulation with antigen. Operationally, these latter two populations can be assayed *in vitro* as CTLp (CTL precursors).

The use of the term "CTL response" to refer to CTL possessing cytolytic activity, and not merely to CTL that could acquire cytolytic activity upon stimulation or restimulation with antigen, is clear in the instant application. For example, the specification discloses that indicators of a CTL response include: (1) a skin test dependent on the presence of highly activated CTL (Specification, at page 12, lines 2-6); (2) specific T-cell frequencies elevated orders of magnitude above a "memory" level (Specification, at page 13, lines 3-5); and (3) positive primary *ex vivo* cytotoxicity (*see, e.g.*, examples, particularly page 63, lines 14-16). (Emphasis added.)

During the typical effector CTL phase of the cytolytic immune response, the population of effector CTL circulating in the body rapidly expands and then diminishes following exposure to antigen, usually peaking after about 7-10 days. If the typical response dynamics of the

population of effector CTL were to be depicted graphically, the graph would show a curve of increasing population or activity with a peak at 7-10 days and a rapid decline from that peak.

In contrast, in a sustained CTL response, the population of effector CTL following exposure to antigen can be graphically represented as an increase and subsequent continued elevation, including, for example, a prolonged peak, a slowed decline, and a partial decline to an above-baseline plateau, rather than the typical initial increase to a peak followed by a rapid decline. Thus, obtaining a sustained CTL response refers to prolonging the effector CTL phase of the cytolytic immune response.

The claimed invention is directed to prolonging the effector CTL phase of the cytolytic immune response. Thus, the claims of the instant application are directed to "obtaining a sustained CTL response." (Emphasis added.) As discussed above, effector CTL are clearly distinguishable from CTLp (including memory CTL), which require stimulation or restimulation with antigen.

Neither Issekutz nor Grohmann discloses a sustained CTL response. Both references measure CTL responses using secondary *in vitro* assays, which measure CTLp as an indicator of the presence of memory CTL. Accordingly, neither reference provides any disclosure indicative of T cell function beyond memory CTL.

Issekutz

The Office Action alleges that Issekutz teaches a method of obtaining a sustained CTL response in a mammal and that the method inherently maintains the antigen in the mammal's lymphatic system over time to induce a sustained CTL response, since lymphoblast output increased for 7 days following virus injection and virus specific cytotoxic T cells were detectable for up to two weeks. The Office Action asserts that "the reference antigen is sustained in the lymph node otherwise the reference CTL response would not have last[ed] over two weeks."

Issekutz discloses subcutaneous injection of a vaccinia virus into the drainage site of a cannulated lymph node. Issekutz at page 516-517, and 521. Thus, the antigen was deposited into an area of tissue just below the skin where it later migrated into the lymph nodes of the subject. The kinetics of the response obtained by Issekutz indicate that lymphoblasts were initially present in only small numbers. The population of lymphoblasts then increased rapidly 70 hours after the

injection to a maximum at 150 hours after the injection. *Id.* at page 517. As shown in Figure 1, the maximum at 150 hours was followed by a sharp decline in the number of lymphoblasts to nearly zero by the end of the two-week measuring period. *Id.* at page 518. This response curve is consistent with a typical effector CTL phase of the cytolytic immune response, in which the population of effector CTL circulating in the body rapidly expands and then diminishes following exposure to antigen, usually peaking after about 7-10 days with a rapid decline from that peak.

In contrast, the claimed invention is directed to obtaining a sustained CTL response, or a prolonged effector CTL phase. Depicted graphically, a sustained CTL response would show an increase and subsequent continued elevation. As discussed above, Issekutz observed a rapid decline in lymphoblast population following the peak at 150 hours, with almost no lymphoblasts detected by the end of the two-week measuring period. Thus, Issekutz does not teach obtaining a sustained CTL response. Instead the data provided in Issekutz demonstrate the "conventional" effector kinetics discussed in Applicants' foregoing Review of CTL Response Kinetics. Accordingly, Applicants respectfully submit that Issekutz cannot anticipate Claims 72, 74, 79-80, 82-84, 87, 89, 90 and 91.

Because Issekutz does not teach, either directly or inherently, each and every element of the claimed invention, Claims 72, 74, 79-80, 82-84, 87, 89, 90 and 91 are novel under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that this rejection be withdrawn.

Grohmann

The Office Action alleges that Grohmann teaches a method of obtaining a sustained CTL response in a mammal comprising injecting minute amounts of cell-free antigen directly into the lymphatic vessel such as the spleen. The Office Action alleges that the direct injection taught by Grohmann inherently sustained a CTL response because the antigen is not being degraded or susceptible to metabolic clearance.

Grohmann discloses the surgical implantation of a nitrocellulose-bound protein in order to elicit a humoral and a cellular immune response. *See* Grohmann at 10. Specifically, antigenic peptide adsorbed on a membrane strip was deposited in the spleen of a mouse through a small incision in the splenic capsule. *Id.* Grohmann reports both increased CTLp and a $CD4^+$ T cell-mediated DTH response. Table I of Grohmann contains data from an *in vitro* assay in which

positively selected CD8+ lymphocytes where stimulated *in vitro* and assayed for cytotoxic activity after 5 days. Accordingly, this assay only examines secondary lytic activity, which is a measure of CTLp as an indicator of memory CTL activity. Table II contains data from a delayed type hypersensitivity (DTH) assay in which the effect of intrasplenic immunization on the expression of DTH reactivity was measured. Grohmann explicitly acknowledges that DTH reactivity is "a cell-mediated *in vivo* response that is known to be mediated by helper/DTH CD4+ lymphocytes." Grohmann at 13 (emphasis added).

This is in contrast to the assays of the instant application, which are designed to detect a sustained CTL response and thus measure the presence and duration of CTL with immediately available activity, or effector CTL, in the animal. As explained above, a sustained CTL response is a CTL response wherein the effector phase is prolonged. Grohmann fails to disclose the presence or duration of the effector phase of the immunologic CTL response. Accordingly, Grohmann cannot teach prolonging the effector phase of the immunologic CTL response. The Office Action's assertion that Grohmann inherently teaches a sustained CTL response because the antigen is not being degraded or susceptible to metabolic clearance is well beyond what the reference states, and is wholly unsupported by the reference. Furthermore, that sustaining an antigen implies sustained CTL activity is nowhere disclosed or even suggested in the reference. Thus, the Office Action's assertion that the reference discloses sustained CTL activity is improper overreaching and over-interpretation by the PTO. Because Grohmann fails to teach obtaining a sustained CTL response, the reference does not anticipate Claims 79-80, 83, 86, 87, and 90.

Because Grohmann does not teach each and every element of the claimed invention, Applicants respectfully request reconsideration and withdrawal of this rejection.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 102(b), and allowance of the pending application.

Rejection Under 35 U.S.C. § 103

The Office Action has rejected Claims 72, 73 and 78 under 35 U.S.C. § 103(a) as being unpatentable over Issekutz in view of Klavinskis *et al.*, *J Immunol* 157(6):2521-7 (1996).

In addition, the Office Action has rejected Claims 72, 75-76, 87 and 88 under 35 U.S.C. § 103(a) as being unpatentable over Issekutz in view of U.S. Patent No. 6,204,250 B1, Coupey *et al. Cytokine* 5(6):564-9 (1993) and Zinkernagel *et al., Immunol Rev* 156:199-209 (1997).

The Office Action has also rejected Claims 72 and 77 under 35 U.S.C. § 103(a) as being unpatentable over Issekutz in view of U.S. Patent No. 5,830,452 A and U.S. Patent No. 5,279,608.

Additionally, the Office Action has rejected Claims 78 and 81 under 35 U.S.C. § 103(a) as being unpatentable over Issekutz in view of U.S. Patent No. 5,830,452 A.

Finally, the Office Action has rejected Claims 83 and 85 under 35 U.S.C. § 103(a) as being unpatentable over Issekutz in view of U.S. Patent No. 6,037,135.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Independent Claims 72, 83, and 87 are directed to obtaining a sustained CTL response. Thus, obtaining a sustained CTL response is a meaningful feature of the claims, and therefore, must be considered in evaluating the patentability of the claims. Issekutz is applied as in the rejection under 35 U.S.C. § 102(b) above. As discussed in response to that rejection, Issekutz demonstrates the "conventional" effector kinetics discussed in Applicants' foregoing Review of CTL Response Kinetics. *See* Issekutz at page 517-18. Thus, the primary reference for each combination, Issekutz, does not teach or suggest obtaining a sustained CTL response. Further, as discussed more fully below, this same feature of the claimed invention, namely, a sustained CTL response, is missing from each of the cited secondary references. It necessarily follows that there is no combination of the references that teaches or suggests this feature. Accordingly, all of the asserted combinations of references fail to satisfy a necessary criterion for establishing a *prima facie* case of obviousness.

Klavinskis

The Office Action asserts that Klavinskis teaches a method of obtaining a sustained CTL response in a mammal such as Rhesus macaques by injecting subcutaneously in the proximity of the iliac lymph node of the macaques a liquid comprising a cell-free antigen such as SIVp27:Ty-VLP mixed with aluminum hydroxide that induce a virus-specific CTL response.

Klavinskis discloses that cells were harvested 7 to 10 days following immunization and cultured in the presence of antigen. Klavinskis at page 2523. Accordingly, this assay only examines secondary lytic activity, which is a measure of CTLp as an indicator of memory CTL activity. Moreover, Klavinskis explicitly states that no primary CTL response was detectable. *Id.* This is in contrast to the assays of the instant application, which measure the presence and duration of CTL with immediately available activity, or effector CTL, in the animal. Klavinskis fails to disclose the presence or duration of the effector CTL phase of a cytolytic immune response. In addition, Klavinskis fails to teach or suggest prolonging the effector CTL phase of the response. Accordingly, because Klavinskis fails to provide any disclosure indicative of T cell function beyond T cell memory, a person of ordinary skill in the art would recognize that the reference does not teach or suggest a sustained CTL response.

The '250 patent

The Office Action characterizes the '250 patent as teaching a method of immunizing a mammal such as an infant against any target antigen delivered in the form of a nucleic acid or vector in the host cell that encodes said antigens such as virus or bacteria. *See* Office Action (citing the '250 patent Abstract, col. 4, col. 7, lines 49-53, and claim 14, in particular).

The '250 patent teaches prophylactic immunization of infants in which an initial immunization using nucleic acid antigen is followed some time later by a booster immunization with live virus. The '250 patent, at col. 8, lines 27-29. The number of inoculations required for the induction of the described effect using the method taught by the '250 patent is "at least one, and is more preferably three" inoculations. The '250 patent, at col. 8, lines 39-44, and col. 9, lines 55-56. The '250 patent does not teach or suggest prolonging the effector CTL phase of the cytolytic immune response between inoculations.

The '250 patent discloses that primary cytotoxicity was observed only after the booster immunization with live virus. *Id.* at col. 11, lines 56-64. However, the '250 patent provides no

disclosure of the post-peak phase of the CTL response following the booster immunization with live virus. In addition, the virus challenge experiments disclosed in the '250 patent, at col. 12, line 26 to col. 13, line 13, are relevant to immunity resulting from the presence of memory CTL, but are not indicative of a sustained CTL response, which requires the presence of effector CTL. Thus, the '250 patent does not disclose prolonging the effector CTL phase of a cytolytic immune response. Accordingly, one of ordinary skill in the art would recognize that the '250 patent does not teach or suggest a sustained CTL response.

Coupey

The Office Action characterizes Coupey as teaching injection of the popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections . Office Action (citing Coupey at page 567, col. 1, & 2, in particular).

Coupey teaches that high titre, highly specific polyclonal anticytokine antibodies can be generated when immunization is performed in the popliteal lymph node using low or very low amounts of purified cytokines. Coupey at page 564. Antibodies are specialized proteins that specifically recognize and bind to one particular protein. They are produced by B lymphocytes in response to foreign antigens. Thus, Coupey looked only at the activity of B lymphocytes.

In contrast, the pending claims are directed to a method of obtaining a sustained cytotoxic T lymphocyte (CTL) response. Thus, the claimed methods concern the activity of T lymphocytes. It is well known in the art that B cell and CTL responses are not comparable. Because Coupey concerns only the activity of B lymphocytes, one of ordinary skill in the art would recognize that Coupey does not teach or suggest a sustained CTL response.

Zinkernagel

The Office Action notes that Zinkernagel teaches that antigen presenting cells (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored. Zinkernagel at page 202, col. 2, in particular.

Zinkernagel teaches that antigen presenting cells transport antigen from the periphery to local organized lymphoid tissue. *Id.* at 199. Zinkernagel provides no disclosure of the kinetics of a CTL response. Thus, Zinkernagel provides no disclosure of the effector CTL phase of a cytolytic immune response, much less prolonging the effector CTL phase of the response. Accordingly, a person of ordinary skill in the art would recognize that Zinkernagel does not teach or suggest a sustained CTL response.

The '452 patent

The Office Action characterizes the '452 patent as teaching a method of obtaining a sustained CTL response, such as anti-tumor efficacy, by administering a cytokine such as IL-2. The Office Action asserts that the '452 patent teaches sustained delivery of any compound of interest using a device external to the mammal such as a computer driven pump. Office Action (citing the '452 patent at col. 5, lines 57-65, in particular). The Office Action asserts that the reference teaches a method of using an external device to enhance the therapeutic index of any compound, such as a cytokine, that is useful to stimulate CTL response such as treating tumors, improving patient compliance and minimizing toxicity. *Id.* (citing the '452 patent Abstract, in particular).

The '452 patent discloses a method for enhancing the therapeutic index of IL-2 treatment, wherein the method is directed to delivering IL-2 to a patient such that the IL-2 concentration in the patients' plasma follows a defined clearance profile. The '452 patent at col. 2, lines 62-66. The '452 patent teaches that once an optimum pharmokinetic curve is described, the attending physician can administer IL-2 by bolus dose, continuous infusion, or constant infusion, intravenously, subcutaneously, intraperitoneally, etc. *Id.* at col. 5, lines 58-63. Thus, the '452 patent addresses enhancing the efficacy of IL-2 treatment by addressing the problems of how long and how often IL-2 is administered to a patient.

The '452 patent does not teach or suggest administering any compounds other than IL-2 to a patient, nor does the reference teach or suggest obtaining a CTL response. Accordingly, one of ordinary skill in the art would recognize that the '452 patent does not teach or suggest a sustained CTL response.

The '608 patent

The Office Action characterizes the '608 patent as disclosing an osmotic pump suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs, analgesics, or combination of agents. Office Action (citing the '608 patent at col. 6, lines 32-35, in particular).

The '608 patent relates to osmotic pumps capable of delivering a fluid over a prolonged period of time. The reference is void of any disclosure relating to obtaining a CTL response, much less obtaining a sustained CTL response. Thus, one of ordinary skill in the art would recognize that the '608 patent does not teach or suggest a sustained CTL response.

The '135 patent

The Office Action characterizes the '135 patent as teaching a method of making a patient matched antigen such as MHC class I peptide that matches with a patient's allele and binds to the TCR for generating the antigen specific cytotoxic T lymphocyte response. The Office Action further asserts that the reference antigen is useful for inducing antigen specific T lymphocyte responses in vaccines against tumors and chronic infections. Office Action (citing the '135 patent at col. 16, lines 62-65, in particular).

The '135 patent discloses methods for making immunogenic peptide compositions. While the reference discloses that the immunogenic compositions are capable of inducing a CTL response, the '135 patent provides no disclosure of the kinetics of the resulting CTL response. Thus, the '135 patent does not specifically discuss the effector CTL phase of a cytolytic immune response, much less teach prolonging the effector CTL phase of the response. Accordingly, a person of skill in the art would recognize that the reference does not teach or suggest a method of obtaining a sustained CTL response.

Because the same feature of the claimed invention, namely, a sustained CTL response, is missing from each of the cited references, it necessarily follows that there is no combination of the references that teaches or suggests this feature. Thus, the cited references, either alone or in combination, do not teach or suggest obtaining a "sustained CTL response." Accordingly, all of the asserted combinations of references fail to satisfy a necessary criterion for establishing a *prima facie* case of obviousness.

For the foregoing reasons, the Office Action has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: April 13, 2004

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